DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
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RECOMBINANT DNA ADVISORY COMMITTEE
WORKING GROUP ON HUMAN GENE THERAPY

MINUTES OF MEETING[1]

DECEMBER 16, 1985

The Working Group on Human Gene Therapy of the Recombinant DNA Advisory Committee was convened at 9:00 a.m. on December 16, 1985, at the National Institutes of Health, Building 31, Conference Room 6, 9000 Rockville Pike, Bethesda, Maryland 20892. Dr. LeRoy Walters was Chair. The following were present for all or part of the meeting:

Working Group members:

W. French Anderson
Judith Areen
Alexander Capron
James Childress
Samuel Gorovitz
Susan Gottesman
Clifford Grobstein
Maurice Mahoney
Arno Motulsky
Robert Rich
Harold Varmus
LeRoy Walters
Anne Witherby
William Gartland
(Executive Secretary)

A working group roster is attached (Attachment I).

Liaison representatives:

Bonnie Lee, Food and Drug Administration
Henry Miller, Food and Drug Administration

Ad hoc consultants:

Samuel Ackerman, Food and Drug Administration
George Scangos, Johns Hopkins University

Other National Institutes of Health staff:

Stanley Barban, NIAID
Prabhakara Choudary, NINCHS
Rachel Levinson, OD
Elizabeth Milewski, NIAID

Others:

Philip Chao, Food and Drug Administration
Jeff Christy, Blue Sheet
Robert Cook-Deegan, Office of Technology Assessment

[1]The working group is advisory to the RAC, and its recommendations should not be considered as final or accepted.

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Dr. Walters convened the meeting of the Working Group on Human Gene Therapy at 9:15 a.m. on December 16, 1985. He said several topics would be covered at this meeting: (1) retroviral vectors; (2) the November 12, 1985, meeting of the RAC Working Group on Viruses; (3) transgenic animal studies; (4) the Food and Drug Administration (FDA) process for filing a "Notice of Claimed Investigational Exemption for a New Drug" (IND); and (5) other issues and announcements.

Retroviral Vectors

Dr. Anderson gave a presentation on the use of retroviral vectors to transfer genes in human gene therapy. He explained that retroviruses are animal viruses with a glycoprotein envelope and an RNA genome that replicate through a DNA intermediate. The DNA intermediate is stably integrated into cellular DNA; the integrated DNA is termed the provirus. Dr. Anderson said at this time many basic retroviral functions are not fully understood.

Dr. Anderson described the retrovirus life cycle (Attachment II). He said the virus recognizes sites on the cell membrane and adsorbs to these receptor sites. After penetration of the cell membrane, the single-stranded RNA genome is reverse transcribed in the cytoplasm to a double-stranded circular DNA molecule. The circular double-stranded molecule is transported into the nucleus and integrates into the host chromosome by a highly efficient ordered process. The integrated provirus serves as the template for synthesis of mRNAs encoding the gag, pol, and env functions as well as full-length transcripts of the viral genome.

Two viral long terminal repeats (LTRs) are situated at the junctions between viral and cellular genomes. Functional and nucleotide sequencing studies of LTRs derived from a number of different retrovirus isolates suggest that LTRs provide a number of functions essential to the retrovirus life cycle. These functions include provirus integration into host DNA, viral DNA synthesis, and transcription of the viral genome. The LTR on the 5' region of the provirus genome contains the functional transcriptional initiation site, while the LTR on the 3' region contains the functional termination signal. Most retrovirus LTRs also include sequences that can enhance the transcriptional activity of flanking viral or cellular DNA. Immediately contiguous to the LTRs are sequences essential for virus DNA synthesis; in addition, a sequence necessary for packaging of the viral RNA genome into nascent virions at the cell membrane is located near the 5' LTR.

The LTRs control three major regions in the virus genome; gag, pol, and env. The gag region codes for four structural proteins used in encapsidation. These proteins bind to 5' regions of the genome. The pol region codes for the reverse transcriptase, an endonuclease which functions in insertion of the provirus into the chromosome, and an endopeptidase. Env genes code for proteins involved in budding of infectious virus particles from the cell.

The gag, pol, and env regions represent a very intricate system with regulatory regions super-imposed on the structural genes. The functions of these control regions have not yet been fully elucidated. In a retroviral vector, some or all of the gag, pol, and env genes are deleted and the gene(s) of interest inserted. The major differences between the various research groups currently developing vectors for human gene therapy are the modifications introduced into these regions.

Dr. Anderson said investigators attempting to engineer retroviral vectors face several problems. The major problem is constructing a "workable" vector. The vector must be introduced into cells of the animals' body, and the gene of interest expressed at reasonable levels. At this time, high expression of these vectors has not been obtained in animals. Vectors which should provide improved expression are being developed, but it is not yet known whether these vectors will have high enough expression levels to be useful in human gene therapy. High levels of expression depend on the control regions and to a lesser extent the introduced gene.

Dr. Anderson said the second issue faced by investigators is whether unanticipated untoward effects may occur. The important considerations in evaluating the possibility of untoward effects are described in detail in the "Points to Consider in the Design and Submission of Human Somatic Cell Gene Therapy Protocols" developed by the working group.

Mr. Capron asked whether untoward events were possible with retroviral vectors since basic retroviral functions are not well understood. He asked Dr. Anderson to offer a hypothetical scenario of such an event. Dr. Anderson said a primary conjectural effect would be induction of cancer through insertional activation of cellular proto-oncogenes.

Dr. Anderson reminded the group that gene therapy would be applied to seriously ill individuals, and risk/benefit considerations would have to be balanced. He said risk is inherent in any procedure. He offered the example of David the "bubble boy." David, who was born with severe combined immune deficiency disease, received a bone marrow tranplant from his sister in the hope that the transplant would reconstitute his immune system. However, David died as a result of the unexpected activation of latent EBV virus in the bone marrow cells of the donor.

Dr. Anderson said data generated with animal systems could be used to predict a probability of inducing carcinogenesis through retrovirus mediated insertional activation. He said the risk of injury is expected to be low based on current experience with animal systems.

Dr. George Scangos of Johns Hopkins University said the important issue of insertional activation arises because the site of retrovirus insertion cannot be controlled, and integration could result in activation of a cellular proto-oncogene. Whether the patient's immune system would be able to control a tumor resulting from activation of a proto-oncogene is not known.

Dr. Anderson suggested such tumors would rarely occur in heterozygous individuals. Problems are not evident in heterozygous transgenic mice; serious problems are evident, however, in homozygous descendants.

Dr. Walters asked whether investigators would be able to detect an untoward event within a few weeks of treatment. Dr. Anderson replied they might.

Dr. Motulsky said the Working Group on Human Gene Therapy would evaluate the possibility of patient injury or spread of recombinant viruses to other people; the points to consider document developed by the working group addresses these issues.

Dr. Rich thought at the present time the risks associated with drug therapies can be evaluated with greater certainty than the risks associated with human gene therapy.

Mr. Capron said the current drug evaluation process is also inexact. Some drugs which appear to be very safe with no evident adverse effects have caused problems in patients several years after administration. Similarly, negative side effects of human gene therapy may not be detected for many years; some diseases caused by retroviruses have a long incubation period. Ultimately, only human studies will demonstrate safety in humans.

Ms. Witherby said two issues impacting on an evaluation of the potential for negative effects are: (1) whether test animals have been followed for a sufficiently long period of time; and (2) whether the effects of the therapy could be controlled or are reversible.

Report on the November 12, 1985, Meeting of the Recombinant DNA Advisory Committee (RAC) Working Group on Viruses

Dr. Walters then asked Dr. Gottesman, the Chair of the Working Group on Viruses, to report on the November 12, 1985, meeting of that working group. Dr. Gottesman said the November 12, 1985, meeting was primarily convened: (1) to respond to scientific issues originating in a memorandum from the Department of Health and Human Services; and (2) to address the impact of recent developments in virology on the NIH Guidelines for Research Involving Recombinant DNA Molecules.

Dr. Gottesman said the major issues discussed by the Working Group on Viruses were: (1) should RNA derived from recombinant DNA be explicitly covered by the NIH Guidelines; (2) should the NIH Guidelines be modified with respect to cloning of small fragments of viruses in tissue culture systems; (3) should the NIH Guidelines be modified to explicitly refer to experiments involving retroviruses; and (4) what safety levels are appropriate for research involving retroviruses?

Dr. Gottesman said currently the NIH Guidelines only refer to recombinant DNA and do not refer to RNA derived from recombinant DNA although RNA viruses would appear to be covered by case law. A proposal addressing RNA derived from recombinant DNA was developed by a RAC working group and reviewed by the Working

Group on Viruses. The Working Group on Viruses thought the proposal was appropriate. This proposal will be presented to the RAC for consideration at the January 27, 1986, meeting.

Dr. Gottesman reported that the Working Group on Viruses felt it would be appropriate to modify the NIH Guidelines to exempt tissue culture experiments involving small fragments of viral genomes. An argument for exempting small pieces of viruses is that few mechanisms exist for spread of these small pieces, and a modification exempting tissue culture experiments involving small pieces of viral genomes would reduce the Institutional Biosafety Committee (IBC) workload.

Dr. Gottesman reported that three important issues were raised during the working group discussion of the status of retroviruses under the NIH Guidelines: (1) Is the virus an infectious or a defective virus? An infectious virus is capable of multiple rounds of replication. Defective viruses usually can only go through one round of replication. Recombinant vectors, including retroviral vectors, are generally defective since the added genetic material replaces information necessary for replication. The NIH Guidelines are generally less concerned about the potential hazard associated with defective viruses. Retroviruses recombine at high frequency, however; and this aspect of their behavior may permit them to generate infectious particles through recombination with helper viruses or endogenous retroviral sequences. The consensus of the group was that while recombination frequency in retroviruses is high, the probability of recombination and the products of such recombinations can generally be predicted. (2) What is the host range of the retrovirus and the derived vector? Some retroviruses have a narrow host range; other retroviruses have a broad host range. Those retroviruses possessing a broad host range present a greater concern. (3) What are the effects of the retroviruses or the derived vectors on the host? For example, is the virus oncogenic or cytotoxic?

Dr. Gottesman said the discussion on appropriate safety levels for research involving retroviruses indicated that most laboratories use Biosafety Level (BL) 2 containment for research involving retroviruses. Some laboratories in addition employ BL3 practices for research with certain viruses. Dr. Gottesman said the Office of Recombinant DNA Activities (ORDA) currently recommends BL2 conditions for research involving retroviral agents.

Dr. Gottesman said no clear consensus emerged at the November 12, 1985, meeting on how the NIH Guidelines should deal with retroviruses or retroviral vectors. All working group members, however, felt some combinations of characteristics should be carefully evaluated. Dr. Gottesman suggested experiments involving retroviruses could be performed under BL2 containment. However, if the vector possesses two of the three characteristics of infectivity, oncogenicity and broad host range, consideration should be given to rising containment to BL3.

Dr. Robert Cook-Deegan of the Office of Technology Assessment asked how Rous sarcoma virus (RSV) would be treated under this proposal. RSV is infectious and oncogenic, but because its host range does not include humans it is not considered a danger to investigators.

Dr. Anderson said a virus should probably possess the three characteristics of infectivity, oncogenicity, and broad host-range before BL3 containment is required.

Dr. Gottesman said the working group also addressed the issue of whether Appendix B, "Classification of Microorganisms on the Basis of Hazard," of the NIH Guidelines should be modified. Appendix B does not classify retroviruses although other types of viruses are classified in this appendix. The working group discussion indicated a preference for language describing the considerations involved in using retroviruses rather than a specific classification of retroviruses in Appendix B of the NIH Guidelines. They felt descriptive language might be more flexible than a listing in Appendix B.

Dr. Walters said a portion of the November 12, 1985, meeting of the Working Group on Viruses was devoted to the vectors to be used in human gene therapy. The working group discussed: (1) vector recombination, and (2) insertional activation or inactivation of chromosomal genes. Dr. Walters said the consensus was that the "Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy Protocols" adequately address these issues.

Dr. Gottesman said the Working Group on Viruses agreed insertional activation or inactivation by human gene therapy vectors are low probability events. They noted, however, that high levels of recombination occur with retroviruses, and this high level of recombination should be considered in developing human gene therapy vectors. Dr. Grobstein said a fourth item of concern may exist, activation of chromosomal genes which are not proto-oncogenes through retrovirus insertion.

Dr. Motulsky said many aspects of retroviral biology are unknown; he questioned whether human gene therapy vectors might produce surprises. He offered the example of HTLV III/LAV; at this time it is not known why certain T-cells are infected and destroyed by the virus while in other patients neural tissue is the target.

Dr. Anderson said HTLV III/LAV has a regulatory system different from that of other retroviruses; the tat gene of HTLV III/LAV is a post-transcriptional activator and apparently activates translation of both its own and the products of other genes. Dr. Gottesman agreed that investigators do not know all the rules regulating retroviral behavior.

Mr. Capron asked whether investigators believe the current hypothetical model of retrovirus functioning is correct. Dr. Anderson felt the model is probably correct since investigators can generally predict the results of experiments based on this model.

Transgenic Animal Studies

Dr. Walters said Dr. Scangos would describe transgenic experiments involving the introduction of foreign DNA into animal genomes.

Dr. Scangos said transgenic animals are made for several reasons: (1) to study tissue and stage-specific gene expression in development; (2) to study phenotypic effects of foreign gene expression; (3) to study oncogene expression; (4) to study insertional mutagenesis; and (5) to produce animal models of human disease. In the future, a sixth reason may be to create transgenic "factory" animals which would produce medically important compounds.

Dr. Scangos said there are four methods of introducing foreign DNA into animals: (1) microinjection of foreign DNA into the blastocoel cavity of early embryos; (2) exposure of early embryos to an infectious retrovirus; (3) transfecting DNA into totipotent teratocarcinoma cells followed by injection of selected cells into the blastocoel; alternatively, nuclei from such cells can be introduced into fertilized eggs from which the pronuclei have been removed; and (4) microinjection of DNA directly into the pronuclei of fertilized eggs.

Dr. Scangos said microinjection of DNA into the pronuclei of fertilized eggs is the technique most used for introducing foreign DNA. Microinjection allows a variety of different DNA molecules to be introduced into the cells of the experimental animals; there is no constraint on the size or the sequence of the DNA to be introduced. Superovulated female mice are mated, and the one-cell embryos of the pronuclear stage are removed from the reproductive tract. The one-cell embryos are stabilized against a blunt-end glass pipette and foreign DNA injected through a fine glass needle into one of the two pronuclei. Approximately 50% of the injected embryos are lost at this point. The surviving microinjected embryos are then implanted in the oviducts of pseudopregnant female mice. Ten to 20% of the implanted embryos develop into mice. Twenty-five percent of these offspring will have incorporated the foreign gene(s) into their genomes. A subset of the animals incorporating the gene into their chromosomes express the foreign gene. The success rate of this technique in obtaining mice expressing the foreign gene is approximately 1 to 3% depending on the season and the mouse strain.

Dr. Scangos said the injected DNA most often integrates into a single chromosomal site; the site of insertion cannot be controlled experimentally. Multiple copies of the injected DNA are typically arranged in the chromosomal insertion site in tandem head-to-tail arrays containing up to several hundred copies; copy number is not under experimental control. The mechanism of integration is not known; the foreign DNA might be incorporated either by recombination or during chromosome repair. Microinjected DNA appears to integrate randomly at any site in the genome including the middle of genes. How multiple copies of the microinjected DNA integrate into the chromosome at a single site is not known. Since multiple copies of the foreign gene are injected into the embryo, one possibility is that one copy of the injected gene may integrate into a chromosomal site; and other copies may subsequently integrate by homologous recombination with the original copy. The other possibility is that long chains of copies of the injected gene form in the cell and subsequently integrate into a single chromosomal site.

Dr. Gorovitz asked whether substances such as restriction enzymes are introduced into the embryos during microinjection. Dr. Scangos replied that only the foreign DNA is injected into the embryos.

Dr. Scangos said transgenic mice usually express foreign genes in a tissue specific pattern. The factors regulating tissue specific expression are not understood, although expression appears to depend on the site of chromosomal insertion with overall regulation of expression determining in which tissues the genes will be expressed. Chromosomal domains appear to have an effect on the level, but do not appear to affect tissue specific expression. It appears that a 200 base pair sequence contiguous with the promotor at the 5' end of the rat elastase 1 gene directs expression specifically to pancreatic tissue.

Dr. Scangos offered some examples of microinjected foreign genes which were expressed in a tissue specific pattern; the rat elastase 1 gene was expressed in pancreatic acinar cells; the human beta-globin gene was expressed in erythroid cells; a mouse/human beta-globin hybrid gene was expressed in erythroid cells; the rat myosin light chain gene was expressed in skeletal muscle; the mouse alphafetoprotein gene was expressed in yolk sac and liver; the mouse kappa light chain (Ig) gene was expressed in B cells; and the mouse mu heavy chain (Ig) was expressed in B and T cells. Levels of expression of these proteins vary in transgenic animals. For example, rat elastase 1 was expressed at a level 1200 percent above endogenous expression; however, only two percent more mouse/human beta-globin was expressed. Gene expression levels vary from mouse to mouse and from gene to gene. The level of expression does not usually correlate with gene copy number.

Dr. Scangos said tumors arising in trangenic animals microinjected with oncogenes ligated to tissue specific regulatory sequences termed "enhancers" appear to be tissue type specific. He then described some of the types of tumors which arise in transgenic individuals. Choroid plexus papillomas develop within six months of birth in mice microinjected with the SV40 virus; pancreatic adenoma results from microinjection of a hybrid gene composed of SV40 sequences and the rat elastase 1 gene; insulinoma results from microinjection of a hybrid gene composed of SV40 sequences and the gene for insulin; hepatocellular carcinoma and insulinoma result from microinjection of a hybrid gene composed of SV40 sequences and sequences of the virus MT (SV40-MT), additional pathology observed in the offspring of animals injected with SV40-MT are peripheral neuropathy and abnormal myelination; mammary carcinoma are observed in lactating females microinjected with the hybrid gene composed of enhancer sequences of mouse mammary tumor virus (MMTV) and the <u>myc</u> gene (MMTV-<u>myc</u>); adrenal neuroblastoma are observed in transgenic individuals expressing <u>JC</u> virus genes, additional observed pathology are central nervous system neuropathy and abnormal myelination.

The enhancer sequences are implicated in directing tumor development in micro-injected animals to certain types of tissues; the tumors do not occur in tissues which would not normally express the gene. For example, transgenic mice bearing the <u>myc</u> gene fused to the enhancer elements of MMTV develop mammary tumors during the second or third pregnancy. Tumors did not develop in other tissues even though the MMTV-myc genes were expressed in other tissues.

Dr. Scangos said a high percentage of the animals expressing these genes transmit the effect to their progeny.

Dr. Scangos said insertional mutagenesis occurs in regions essential to viability in transgenic animals at a fairly high frequency. The effects of insertional mutagenesis are usually not evident in heterozygous animals. When transgenic animals are inbred, homozygous offspring display these lethal mutations. The available data suggest that 20% of transgenic mice may harbor recessive insertional mutations of essential genes.

Three phenotypes observed with insertional mutagenesis in homozygous animals are: (1) embryonic death; (2) male sterility; and (3) limb deformity. One embryonic lethal mutation arose from insertion of murine leukemia virus in the alpha 1 collagen gene.

Dr. Motulsky asked if there are any examples of a heterozygous dominant arising from insertional mutagenesis. Dr. Scangos said he had heard of a case in which the product of the introduced gene was toxic.

Dr. Scangos said transgenic animals have provided two disease models: (1) transgenic animals obtained through microinjection of the gene coding for the hepatitis B surface antigen mimic chronic carriers of hepatitis B; and (2) animals expressing the JC virus mimic the pathology of progressive multifocal leukoencephalopathy.

Mr. Capron said the human growth hormone gene has been microinjected into animals; he asked Dr. Scangos to comment on these experiments. Dr. Scangos said the human growth hormone gene had been microinjected into sheep, pig, mice, and rabbit embryos. The pigs expressed the gene; however, they were not affected by expression of the human growth hormone gene and grew to normal size. The mice also expressed the gene and grew to larger than normal size.

Dr. Scangos then described the experiments in which the human growth hormone gene was microinjected into mice. The human growth hormone gene was engineered to be under the control of the regulatory sequences of a metallothionein gene. The metallothioneins bind heavy metals such as copper, zinc, cadmium, and mercury and the expression of these genes is increased by the presence of heavy metals in the diet. The diets of mice microinjected with the human growth hormone gene were supplemented by zinc. The mice expressed the human growth hormone gene in tissues that normally synthesize metallothionein and grew to more than normal size; however, since the normal feedback control mechanisms were bypassed, the animals expressed many secondary effects such as pituitary abnormalities, abnormal liver function, and female infertility. The investigators injected subsequent groups of embryos with a fusion gene composed of a metallothionein promotor and the structural gene for growth hormone releasing factor. This fusion gene also stimulates growth of mice but by a different mechanism through elevation of endogenous growth hormone production. Some of the side effects of excess growth hormone production were alleviated by this strategy.

Mr. Capron asked whether microinjected transgenic animals which do not pass the foreign gene to their offspring have been observed. Dr. Scangos said some animals do not pass the foreign gene to their offspring; whether the gene will be passed to progeny depends on the time at which the microinjected DNA integrates into the chromosomal DNA. If chromosomal integration occurs at the pronuclear stage, the gene will be passed to offspring since all cells will contain the insert. If the gene does not integrate until several cell divisions have occurred, the gene will not be present in all the cells of the body and may not be contained in germ line tissue. The gene then will not be passed to offspring.

Dr. Scangos said cells in tissue culture have also been microinjected with foreign DNA. More than half of the cells surviving microinjection express the injected gene(s).

Dr. Scangos said when retroviruses are used to produce transgenic mice, generally only single copies of the viral DNA integrate and integration occurs at a single site within the chromosomal DNA. The insertion site is not under experimental control. Retroviral infection is usually initiated at later embryonic stages resulting in mosaic founder animals; outbreeding of the founder animal is therefore necessary to establish pure lines hemizygous for a single insertion site. Few embryos are lost when foreign DNA is introduced by retrovirus infection. An efficiency of approximately 25% is possible with viral vectors when they are used to infect preimplantation embryos.

Dr. Motulsky said use of microinjection techniques would not be ethically feasible in human subjects. The tremendous embryo losses associated with the microinjection technique would not be acceptable. In addition, it is not possible to determine whether the egg is normal at the pronuclei stage. For most human recessive diseases, three fertilized eggs out of four would be normal for the trait in question. In order for all the fertilized eggs to possess the recessive trait, both mates would have to be homozygous for the deleterious trait. In humans, such a situation is highly unusual.

Dr. Mahoney suggested the embryo could be tested at the 8 cell stage when one cell could be sacrificed to test for the homozygous presence of the deleterious gene. If some cells were modified at early embryonic stages, an individual mosaic for the trait could develop. 'In humans, mosaic individuals frequently do not display disease symptoms although they are carriers.

Dr. Anderson said the microinjection technique is only successful at the pronuclear stage of development. The cell is designed to keep DNA out of the nuclei once the pronuclei fuse.

The working group agreed transgenic germ line modifying procedures are not feasible or acceptable for humans at this time.

The FDA IND Process

Dr. Walters asked Dr. Samuel Ackerman of the Bureau of Drugs and Biologics of the FDA to describe to the working group the process of filing a "Notice of Claimed Investigational Exemption for a New Drug (IND)."

Dr. Ackerman said biologics are defined as materials that come from the blood, except for hormones, and materials that come from microorganisms. The Bureau of Biologics is responsible for products such as albumin, viral vaccines, and bacterial vaccines. The Bureau also has jurisdiction over a number of products produced by biotechnology such as monoclonal antibodies, cytokines, and anti-HTLV III test kits.

Dr. Ackerman said the Bureau of Drugs and Biologics is responsible for regulating investigational stages in drug testing, commercial approval of drugs, and periodic examination of products. An IND (Attachment III) must be filed if any of the products used in a procedure are transported across state lines.

Dr. Ackerman said the IND mechanism primarily monitors clinical trials where the major goal is to demonstrate product safety and efficacy. When clinical trials demonstrate safety and efficacy, the product can be licensed, and the commercial production phase begun. The FDA is then responsible for reviewing the integrity of the production process, the facility, and any changes in the manufactured product.

Dr. Ackerman said the IND is keyed to the product and not to the process or the investigator. Indeed, several different investigational groups can file a single IND. The IND is confidential; its existence cannot be divulged, although a Freedom of Information request can be filed to obtain certain information.

Dr. Ackerman then described the information requested by the IND form. Items one through five deal with the preparation and manufacture of the product, and address issues such as identity, components, source, preparation, purity, strength, reproducibility, stability of material, etc. The sixth item requests all available information derived from preclinical investigations, clinical studies, and experience with the drug. Items seven through ten deal with the proposed clinical investigation. Item seven requests an accurate description of prior investigations and experiences and results pertinent to the safety and efficacy of the drug under the conditions of the investigation; it also requests a description of all relevant hazards, contraindications, side-effects, and precautions suggested by prior investigations and experience with the drug or related drugs. The eighth item requests a description of the scientific training and experience considered appropriate to qualify the investigators or suitable experts to investigate the drug or biologic. The ninth item requests the names, training, and experience of each investigator. The tenth item requests an outline of any phase or phases of the planned investigations and a description of the Institutional Review Board (IRB). The eleventh item requests an agreement that the investigator will notify the FDA if the investigation is discontinued and the reason for discontinuance. Items 12 through 16 deal with notification issues and environmental assessments.

Dr. Ackerman said investigators must file an additional form (Attachment IV) with the FDA as part of an IND application. This form requests information on the principal investigators' qualifications and experience, the requirements of the IRB, and the investigational plan. Item four specifically links the principal investigator to the sponsoring organization which is linked to the FDA and requires that progress reports be made to the FDA at intervals of time not exceeding one year. Any adverse effect that may be regarded as caused by or probably caused by the new drug shall be reported to the sponsor promptly. If the adverse effect is alarming, it shall be reported immediately. Dr. Ackerman said promptly is defined as within seven to ten days and immediately by telephone call.

Mr. Capron asked for the FDA definition of "adverse effect." Dr. Ackerman said the definition of adverse effect is in a constant state of evolution. One camp believes that any effect occurring within thirty days of administration of a drug should be reported. The other camp believes the only effects which need to be reported are those that could with a high degree of confidence be related to the drug. In practice in the beginning stages of a clinical trial, almost every effect is reported; as experience with the drug is gained, fewer observations are reported.

Dr. Gorovitz asked how FDA defines adequacy and safety; some drugs are not safe but are used in desperate cases. Dr. Ackerman replied that adverse effects of a drug are evaluated on a risk/benefit basis. The cases can be highly specific.

Dr. Cook-Deegan asked what criteria trigger FDA involvement in the development of a drug. Dr. Ackerman said FDA can interact at several levels and can issue: regulations; guidelines binding in the legal sense; or points to consider which are less binding and more of an exchange of views. The points to consider documents list FDA concerns and are generally documents in evolution. FDA is considering generating a points to consider document for human gene therapy. A number of triggers exist for initiating such an FDA action. For example, the number of individuals who are involved in the area is one such trigger; another trigger is the amount of controversy surrounding a procedure.

Dr. Ackerman said the FDA attempts to anticipate problems but will not adopt review procedures based on conjecture since such procedures may ultimately impede the review process. Although FDA would like to have some basis for discussion, some experience is needed to develop a reasonable document.

Dr. Motulsky asked how FDA would treat studies such as the National Institutes of Health (NIH) study involving interleukin 2 (IL-2) activation of cancer patient T-cells. Dr. Ackerman replied that procedure involves an autologous transplant of bone marrow cells treated with a biologic and as such falls under FDA jurisdiction.

Mr. Capron asked whether FDA regulates a single investigator treating a single patient. Dr. Ackerman said in some instances, FDA regulates the individual researcher; human gene therapy may be one such instance. Institutions such as the funding agency, the IRB, the medical school, or the pharmacy compounding the substances used in a protocol also may require the investigator to file an IND. FDA welcomes voluntary IND filings and will encourage investigators to file for human gene therapy protocols.

Dr. Cook-Deegan asked how FDA would proceed on receipt of an IND on human gene therapy. Dr. Ackerman said FDA would first perform a cursory examination of the IND for completeness; FDA scientific staff would evaluate the IND with regard to safety issues and would also examine the manufacturing process. The IND would be routed through the FDA review divisions and the relevant scientific divisions. The scientific divisions include virology, blood and blood products, vaccines, biochemistry and biophysics, and quality control.

Dr. Mahoney asked whether the Working Group on Human Gene Therapy and the FDA could become involved in a jurisdictional dispute. Dr. Walters said the working group and RAC have established a process for review of NIH funded protocols.

Dr. Mahoney asked whether a duplication of effort may occur. Ms. Areen thought the working group and FDA would not perform duplicative reviews since the two groups will be evaluating proposals from two different perspectives. Dr. Walters agreed; he pointed out that FDA will handle submissions in a confidential manner. The NIH working group is part of a public process. In this sense, the two groups will perform different functions. Dr. Gorovitz also agreed that different types of issues will be raised by the two groups; the NIH has its agenda while the FDA has its own interests.

Dr. Mahoney asked whether one group might approve of a protocol and the other group disapprove. Dr. Ackerman said the FDA frequently reviews clinical trials developed by the NIH. No problems in coordinating these reviews has arisen in the past. Dr. Bonnie Lee of the FDA said NIH sponsored research involving FDA approved substances currently is reviewed by both the NIH and the FDA. Such review is complementary.

Mr. Capron suggested the NIH process could serve to alert investigators to FDA requirements and procedures.

Dr. Anderson said investigators might wish to submit partial information to FDA in a confidential process rather than wait until a complete protocol is ready for submission. He asked if an informal cooperative discussion process would be useful to the FDA. Dr. Ackerman said there are a variety of mechanisms for communicating with the FDA short of a formal IND submission; e.g., FDA can arrange pre-IND meetings or conferences. He felt these confidential mechanisms would be useful to investigators contemplating human gene therapy.

Dr. Motulsky said FDA oversight is required at the development and commercialization stages. He questioned, however, whether FDA oversight was necessary for early experimental stages of a protocol. He argued that FDA oversight would not be necessary for this stage if the NIH and the RAC working groups were providing oversight.

Ms. Areen said FDA is constrained by law to regulate certain procedures and must adhere to these statutes. Mr. Capron said FDA may be able to proceed with greater rapidity than NIH in reviewing human gene therapy protocols.

Dr. Gorovitz thought the proposals submitted to FDA and to NIH for review could employ an identical format, but the substantive evaluation of the proposals would be different in the agencies. Dr. Ackerman said although the issues may be the same, the emphasis will not be the same; and the reviews would not be well served by use of an identical format.

Dr. Anderson said the Working Group on Human Gene Therapy attempted in its Points to Consider document to take account of the points addressed in an FDA review; the concepts included in the working group document correspond to the concepts in an IND.

Dr. Gartland asked if FDA either approves or disapproves of an IND. Dr. Ackerman replied that INDs are either active or inactive; the IND is related to the product not to the particular study.

Dr. Gartland asked what type of action FDA could take if an investigator proceeds in the absence of FDA approval. Dr. Ackerman said FDA could inactivate the IND and disqualify the investigator from participation in clinical protocols. FDA might also take legal action. Ms. Areen added that subjects participating in a protocol with an inactive IND could sue the investigator.

Other Issues

Dr. Walters informed the working group that President Reagan's veto of the NIH appropriations bill had been overridden by the Senate. This bill contains language for the establishment of a "Biomedical Ethics Board." One of the first studies of this board will be human applications of genetic technologies.

Dr. Walters also announced the procedure the NIH and the Working Group on Human Gene Therapy would follow in dealing with consent forms. He said the NIH does not generally review consent forms since the Office of Protection Against Research Risks (OPRR) is too small to review all the forms associated with NIH funded protocols. Nonetheless, OPRR does review approximately 200 forms a year. The NIH would not prevent the working group from requesting consent forms for the earliest gene therapy protocols, and the working group will request and review these forms.

Ms. Witherby thought the consent form would have an important impact on the working group's decision. Mr. Capron thought it would be a disservice to the NIH not to review the consent form since in the absence of such review the NIH cannot be assured it is providing the appropriate level of care. Dr. Ackerman said the FDA will probably request submission of the consent form as part of the IND process for human gene therapy protocols.

Dr. Walters said one issue the working group should address is the sequence of review; would a protocol require local IBC and IRB approval before submission to the working group.

Dr. Motulsky thought it illogical that the groups which have the least experience with human gene therapy, the local IRBs and IBCs, are the groups which are required to perform the first reviews. Dr. Gottesman said the points to consider document indicates IRBs and IBCs may condition approval on RAC approval.

Dr. Gottesman said one suggestion the Working Group on Viruses considered was whether NIH could certify vectors for use in human gene therapy protocols. While she did not think vector certification would speed up the review process, she suggested the Working Group for Human Gene Therapy could extend to investigators the option of submitting preclinical data on vector construction for review before the clinical protocol is submitted.

Ms. Areen thought the working group should not delay IBC review of protocols for a working group dialogue on vectors. Dr. Grobstein did not think the working group should review preclinical data independent of the protocol; the vectors should be considered in the context of the whole protocol. Dr. Mahoney said he would not wish this process to be seen as a negotiating process between investigators and the working group. Dr. Childress thought the working group process should encourage an information exchange but should not approve portions of experiments.

Dr. Walters said the working group could indicate review of vector data is part of the working group self-education effort. Dr. Anderson suggested a memorandum indicating this position should be published in the Federal Register in order to alert investigators to the working group's position. Ms. Areen suggested working group memoranda could also alert IBCs and IRBs of the working group's position.

Dr. Walters then asked the working group to consider the scheduling of the next working group meetings. He said the next RAC meetings are scheduled for January 27, 1986; May 12, 1986; and September 29, 1986. He suggested the working group schedule their meetings to coincide with the RAC meeting schedule.

Dr. Gartland said ORDA would telephone the members of the working group in order to select meeting dates. He offered the working group a schedule (Attachment V) showing the deadlines for proposal submission prior to a RAC meeting.

Dr. Grobstein suggested a more detailed discussion of the time-line for scheduling meetings might be held at the next working group meeting in light of clincians' experience with clinical trials.

Dr. Gottesman said the working group might at some meeting address the issue of what constitutes a minor modification of a protocol.

Dr. Motulsky suggested the working group also discuss how confidential information should be handled; he could imagine cases where confidential information disclosed in one proposal might affect review of other proposals.

Ms. Areen suggested the working group might consider how the group would proceed on receipt of a report of a harmful effect. Would the working group be called into session to address the issue, the impact of the harmful effect on the protocol, and the impact on other protocols?

Dr. Walters asked the working group whether they would approve of the formation of a subgroup to develop a document describing in lay terminology the purpose of the points to consider document and the working group. The second issue which could be evaluated is whether the points to consider have reached the appropriate audience.

Ms. Witherby said she would like to see a "lay" statement describing the working group's agenda. She agreed to attempt to write a first draft for such a statement.

Dr. Walters adjourned the meeting of the Working Group on Human Gene Therapy at 3:35 p.m. on December 16, 1985.

Respectfully submitted,

Elizabeth Milewski

Elizabeth A. Milewski, Ph.D.
Rapporteur

William J. Gartland

William J. Gartland, Jr., Ph.D.
Executive Secretary

I hereby certify that, to the best of my knowledge, the foregoing Minutes and Attachments are accurate and complete.

5/12/86
Date

LeRoy Walters

LeRoy Walters, Ph.D.
Chair

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WORKING GROUP ON HUMAN GENE THERAPY

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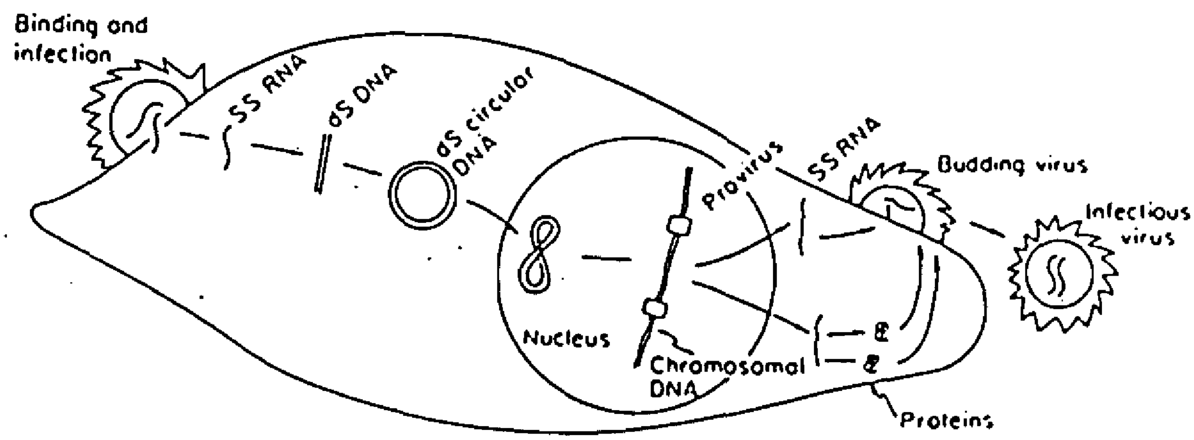

From: Gene Transfer with Retrovirus Vectors. Bernstein, A., S. Berger, D. Huszar, and J. Dick. 1985. In Genetic Engineering: Principles and Methods, Vol. 7. (Ed. J. K. Setlow and A. Hollaender). Plenum Publishing Corporation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved; OMB No. 0910-0014
Expiration Date: February 29, 1984.

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

NOTE: No drug may be shipped or study initiated unless a complete statement has been received. *(21 CFR 312.1(a)(2)).*

Name of Sponsor ____________________ Date ____________

Address ____________________ Telephone (   ) ____________

Name of Investigational Drug ____________________

FOR A DRUG:

Food And Drug Administration
Office of New Drug Evaluation *(HFN-106)*
5600 Fishers Lane
Rockville, Maryland 20857

FOR A BIOLOGIC:

Food and Drug Administration
Office of Biologics *(HFN-823)*
8800 Rockville Pike
Bethesda, Maryland 20205

Dear Sir:

The sponsor, ____________________, submits *this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal* Food, Drug, and Cosmetic Act and §312.1 of Title 21 of the Code of Federal Regulations.

Attached hereto in triplicate are:

1. The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered. (If the drug has only a code name, enough information should be supplied to identify the drug.)

2. Complete list of components of the drug, including any reasonable alternates for inactive components.

3. Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage.

4. Description of source and preparation of, any new-drug substances used as components, including the name and address of each supplier or processor, other than the sponsor, or each new-drug substance.

5. A statement of the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug.

6. A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies and experience with the drug as follows:

a. Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug: Such information should include identification of the person who conducted each investigation; identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection; and enough details about the investigations to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing. When this information, the outline of the plan of clinical pharmacology, or any progress report on the clinical pharmacology, indicates a need for full review of the preclinical data before a clinical trial is undertaken, the Department will notify the sponsor to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified. The Food and Drug Administration will be prepared to confer with the sponsor concerning this action.

b. If the drug has been marketed commercially or investigated (e.g. outside the United States), complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug.

c. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigations and experience with its components, including all reports available to the sponsor suggesting side-effects, contraindications, and ineffectiveness in use of such components: Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration. Include a statement of the expected pharmacological effects of the combination.

d. If the drug is a radioactive drug, sufficient data must be available from animal studies or previous human studies to allow a reasonable calculation of radiation absorbed dose upon administration to a human being.

7. A total (one in each of the three copies of the notice) of all informational material, including label and labeling, which is to be supplied to each investigator: This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications, side-effects, and precautions suggested by prior investigations and experience with the drug under investigation and related drugs for the information of clinical investigators.

8. The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug, bearing in mind what is known about the pharmacological action of the drug and the phase of the investigational program that is to be undertaken.

9. The names and a summary of the training and experience of each investigator and of the individual charged with monitoring the progress of the investigation and evaluating the evidence of safety and effectiveness of the drug as it is received from the investigators, together with a statement that the sponsor has obtained from each investigator a completed and signed form, as provided in subparagraph (12) or (13) of this paragraph, and that the investigator is qualified by scientific training and experience as an appropriate expert to under-

take the phase of the investigation outlined in section 10 of the "Notice of Claimed Investigational Exemption for a New Drug." (In crucial situations, phase 3 investigators may be added and this form supplemented by rapid communication methods, and the signed Form FD-1573 shall be obtained promptly thereafter.)

10. An outline of any phase or phases of the planned investigations and a description of the institutional review committee, as follows:

a. Clinical pharmacology. This is ordinarily divided into two phases: Phase I starts when the new drug is first introduced into man - only animal and in vitro data are available - with the purpose of determining human toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range; phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes. A general outline of these phases shall be submitted, identifying the investigator or investigators, the hospitals or research facilities where the clinical pharmacology will be undertaken, any expert committees or panels to be utilized, the maximum number of subjects to be involved, and the estimated duration of these early phases of investigation. Modification of the experimental design on the basis of experience gained need be reported only in the progress reports on these early phases, or in the development of the plan for the clinical trial, phase 3. The first two phases may overlap and, when indicated, may require additional animal data before these phases can be completed or phase can be undertaken. Such animal tests shall be designed to take into account the expected duration of administration of the drug to human beings, the age groups and physical status, as for example, infants, pregnant women, premenopausal women, of those human beings to whom the drug may be administered, unless this has already been done in the original animal studies. If a drug is a radioactive drug, the clinical pharmacology phase must include studies which will obtain sufficient data for dosimetry calculations. These studies should evaluate the excretion, whole body retention, and organ distribution of the radioactive material.

b. Clinical trial. This phase 3 provides the assessment of the drug's safety and effectiveness and optimum dosage schedules in the diagnosis, treatment, or prophylaxis of groups of subjects involving a given disease or condition. A reasonable protocol is developed on the basis of the facts accumulated in the earlier phases, including completed and submitted animal studies. This phase is conducted by separate groups following the same protocol (with reasonable variations and alternatives permitted by the plan) to produce well-controlled clinical data. For this phase, the following data shall be submitted:

i. The names and addresses of the investigators. (Additional investigators may be added.)

ii. The specific nature of the investigations to be conducted, together with information or case report forms to show the scope and detail of the planned clinical observations and the clinical laboratory tests to be made and reported.

iii. The approximate number of subjects (a reasonable range of subjects is permissible and additions may be made), and criteria proposed for subject selection by age, sex, and condition.

iv. The estimated duration of the clinical trial and the intervals, not exceeding 1 year, at which progress reports showing the results of the investigations will be submitted to the Food and Drug Administration.

c. Institutional review board (IRB). The sponsor must give assurance that an IRB that complies with the requirements set forth in Part 56 of this chapter will be responsible for the initial and continuing review and approval of the proposed clinical study. The sponsor must also provide assurance that the investigators will report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and that the investigators will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazard to the human subjects. FDA will regard the signing of the Form FDA-1571 as providing the necessary assurances above.

(The notice of claimed investigational exemption may be limited to any one or more phases, provided the outline of the additional phase or phases is submitted before such additional phases begin. A limitation on an exemption does not preclude continuing a subject on the drug from phase 2 to phase 3 without interruption while the plan for phase 3 is being developed.)

Ordinarily, a plan for clinical trial will not be regarded as reasonable unless, among other things, it provides for more than one independent competent investigator to maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated, and comparable records on any individuals employed as controls. These records shall be individual records for each subject maintained to include adequate information pertaining to each, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, adequate information concerning any other treatment given and a full statement of any adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation.

11. A statement that the sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason therefor.

12. A statement that the sponsor will notify each investigator if a new-drug application is approved, or if the investigation is discontinued.

13. If the drug is to be sold, a full explanation why sale is required and should not be regarded as the commercialization of a new drug for which an application is not approved.

14. A statement that the sponsor assures that clinical studies in humans will not be initiated prior to 30 days after the date of receipt of the notice by the Food and Drug Administration and that he will continue to withhold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days. If such request is made, the sponsor will be provided specific information as to the deficiencies and will be afforded a conference on request. The 30-day delay may be waived by the Food and Drug Administration upon a showing of good reason for such waiver; and for investigations subject to institutional review committee approval as described in item 10c above, and additional statement assuring that the investigation will not be initiated prior to approval of the study by such committee.

15. When requested by the agency, an environmental impact analysis report pursuant to § 25.1 of this chapter.

16. A statement that all nonclinical laboratory studies have been, or will be, conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if such studies have not been conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in conducting the study and those required in the regulations.

Very truly yours,

SPONSOR	PER
	INDICATE AUTHORITY

(This notice may be amended or supplemented from time to time on the basis of the experience gained with the new drug. Progress reports may be used to update the notice.)

ALL NOTICES AND CORRESPONDENCE SHOULD BE SUBMITTED IN TRIPLICATE.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR

Form approved; OMB No. 0910-0013
Expiration Date: December 31, 1984.

Note: No drug may be shipped or study initiated unless a completed statement has been received *(21 CFR 312.1(a)(12))*.

TO: SUPPLIER OF DRUG *(Name, address, and Zip Code)*

NAME OF INVESTIGATOR *(Print or Type)*

DATE

NAME OF DRUG

Dear Sir:

The undersigned, ______________________________

submits this statement as required by section 505(i) of the Federal Food, Drug, and Cosmetic Act and §312.1 of Title 21 of the Code of Federal Regulations as a condition for receiving and conducting clinical investigations with a new drug limited by Federal *(or United States)* law to investigational use.

1. THE FOLLOWING IS A STATEMENT OF MY EDUCATION AND EXPERIENCE:

a. COLLEGES, UNIVERSITIES, AND MEDICAL OR OTHER PROFESSIONAL SCHOOLS ATTENDED, WITH DATES OF ATTENDANCE, DEGREES, AND DATES DEGREES WERE AWARDED

b. POSTGRADUATE MEDICAL OR OTHER PROFESSIONAL TRAINING. GIVE DATES, NAMES OF INSTITUTIONS, AND NATURE OF TRAINING.

c. TEACHING OR RESEARCH EXPERIENCE. GIVE DATES, INSTITUTIONS, AND BRIEF DESCRIPTION OF EXPERIENCE.

d. EXPERIENCE IN MEDICAL PRACTICE OR OTHER PROFESSIONAL EXPERIENCE. GIVE DATES, INSTITUTIONAL AFFILIATIONS, NATURE OF PRACTICE, OR OTHER PROFESSIONAL EXPERIENCE.

e. REPRESENTATIVE LIST OF PERTINENT MEDICAL OR OTHER SCIENTIFIC PUBLICATIONS. GIVE TITLES OF ARTICLES, NAME OF PUBLICATIONS AND VOLUME, PAGE NUMBER, AND DATE.

IF THIS INFORMATION HAS PREVIOUSLY BEEN SUBMITTED TO THE SPONSOR, IT MAY BE REFERRED TO AND ANY ADDITIONS MADE TO BRING IT UP-TO-DATE.

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2a. The investigator assures that an IRB that complies with the requirements set forth in Part 56 of this chapter will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator also assures that he/she will report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and that he/she will not make any changes in the research that would increase the risks to human subjects without IRB approval. FDA will regard the signing of the Form FDA 1573 as providing the necessary assurances stated above.

b. A description of any clinical laboratory facilities that will be used. (If this information has been submitted to the sponsor and reported by him on Form FDA 1571, reference to the previous submission will be adequate).

3. *The investigational drug will be used by the undersigned or under his supervision in accordance with the plan of investigation described as follows: (Outline the plan of investigation including approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; clinical uses to be investigated; characteristics of subjects by age, sex and condition; the kind of clinical observations and laboratory tests to be undertaken prior to, during, and after administration of the drug; the estimated duration of the investigation; and a description or copies of report forms to be used to maintain an adequate record of the observations and test results obtained. This plan may include reasonable alternates and variations and should be supplemented or amended when any significant change in direction or scope of the investigation is undertaken.)*

4. THE UNDERSIGNED UNDERSTANDS THAT THE FOLLOWING CONDITIONS, GENERALLY APPLICABLE TO NEW DRUGS FOR INVESTIGATIONAL USE, GOVERN HIS RECEIPTS AND USE OF THIS INVESTIGATIONAL DRUG:

a. The sponsor is required to supply the investigator with full information concerning the preclinical investigations that justify clinical trials, together with fully informative material describing any prior investigations and experience and any possible hazards, contraindications, side-effects, and precautions to be taken into account in the course of the investigation.

b. The investigator is required to maintain adequate records of the disposition of all receipts of the drug, including dates, quantities, and use by subjects, and if the investigation is terminated, suspended, discontinued, or completed, to return to the sponsor any unused supply of the drug. If the investigational drug is subject to the Comprehensive Drug Abuse Prevention and Control Act of 1970, adequate precautions must be taken including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

c. The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the drug or employed as a control in the investigation.

d. The investigator is required to furnish his reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained by various investigators. The sponsor is required to present progress reports to the Food and Drug Administration at appropriate intervals not exceeding 1 year. Any adverse effect that may reasonably be regarded as caused by, or probably caused by, the new drug shall be reported to the sponsor promptly, and if the adverse effect is alarming, it shall be reported immediately. An adequate report of the investigation should be furnished to the sponsor shortly after completion of the investigation.

e. The investigator shall maintain the records of disposition of the drug and the case histories described above for a period of 2 years following the date a new-drug application is approved for the drug; or if the application is not approved, until 2 years after the investigation is discontinued. Upon the request of a scientifically trained and properly authorized employee of the Department, at reasonable times, the investigator will make such records available for inspection and copying. The subjects' names need not be divulged unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual cases studied, or do not represent actual results obtained.

f. The investigator certifies that the drug will be administered only to subjects under his personal supervision or under the supervision of the following investigators responsible to him,

____

____

____

and that the drug will not be supplied to any other investigator or to any clinic for administration to subjects.

g. The investigator certifies that he will inform any subjects including subjects used as controls, or their representatives, that drugs are being used for investigational purposes, and will obtain the consent of the subjects, or their representatives, except where this is not feasible or, in the investigator's professional judgment, is contrary to the best interests of the subjects.

h. The investigator is required to assure the sponsor that for investigations subject to an institutional review requirement under Part 56 of this chapter the studies will not be initiated until the institutional review board has reviewed and approved the study. (The organization and procedure requirements for such a board as set forth in Part 56 should be explained to the investigator by the sponsor.)

Very truly yours,

Name of Investigator ____________________

Address ____________________ Telephone (   ) ________

____

(This form should be supplemented or amended from time to time if new subjects are added or if significant changes are made in the plan of investigation.)

★ U.S.GPO:1984-0-464-304/10776

Attachment V

HUMAN GENE THERAPY PROPOSALS
APPROXIMATE REVIEW SCHEDULE (IN WEEKS)

-16	-13	-7	-6	0
Receipt of proposal by NIH	Completion of <u>Federal Register</u> notice for Working Group Meeting	Working Group Meeting	Completion of <u>Federal Register</u> notice for RAC meeting	RAC meeting